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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,320	06/12/2001	Ajay Hasmukhlal Upadhyay	RD 01022	5176

7590 10/25/2010

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ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
10/25/2010	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/879,320
Filing Date: June 12, 2001
Appellant(s): UPADHYAY, AJAY HASMUKHLAL

Thomas Pavelko
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8 appealing from the Office action mailed 6-8-10.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 2-4, 33-34 and 37 are pending.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

6,372,252	Blume et al	4-2002
5,032,406	Dansereau et al.	7-1991
3,627,583	Troy et al.	12-1971
6,623,756	Wilber et al.	9-2003

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 2-4, 8, 33, 34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,372,252 to Blume et al (Blume) in view of US 5,032,406 to Dansereau et al (Dansereau), US 3,627,583 to Troy et al and US 6,623,756 to Wilber et al (Wilber) or US 6,372,252 to Blume et al (Blume) in view of US 5,032,406 to Dansereau et al (Dansereau) and US 6,623,756 to Wilber et al (Wilber.

Blume teaches immediate and sustained release formulations comprising guaifenesin. Blume teaches loading guaifenesin and methocel into a high shear mixer, mixed at high speed, adding water and further mixing at additional time to complete granulation. The composition is next dried in fluid dryer and then passed through a mill fitted a suitable size screen (col. 7, lines 63 through col. 8, lines 23). Thus, the resulting

material of Blume reads on agglomerated mixture because the processing of the material involves the same steps as described in the instant application (page 14, example 1 and 2- page 15, line 14). Blume fails to teach granulation of guaifenesin with polyvinylpyrrolidone.

Dansereau teaches a tablet composition that provides dual action, for immediate and sustained release, comprising an outer tablet and an inner tablet respectively. The active ingredient of both inner and outer tablets comprises guaifenesin. The inner tablet particularly comprises guaifenesin and polyvinylpyrrolidone (PVP) (example I, col. 6) and is made by oscillating guaifenesin and half of the PVP through a mesh screen. The blend is then transferred to a blender and mixed until uniform consistency and granulated with PVP that is previously dissolved in water to form 8% to 12% PVP. The mixture is dried and oscillated through a 12 mesh screen and returned to the blender. The remaining PVP, microcrystalline cellulose and talc are added to the dried granulation and mixed for uniform consistency. Finally, zinc stearate is added and the mixture is mixed until it is of uniform consistency. The mixture is then compressed into inner tablets using a standard tablet press. Thus, the resulting inner tablet composition of Dansereau read on the claimed agglomerate mixture because the process involves the same steps as described in the instant specification (page 3, lines 15-20). Dansereau fails to teach the claimed particle sizes.

Wilber teaches tablets for controlled release of a desired drug that are directly compressed from a flowable, compressible mixture of the drug and a rheology modifying polymer or a copolymer and additional excipients (abstract). The rheology

modifier is a homopolymer or copolymer is processed into a desirable granular size by compacting into large agglomerates or aggregates and subsequently fractured into smaller granules and screened to suitable particle size of low amounts of dust (col. 1, L 40-44). The granulated rheology polymers and copolymers desirably have a specific particle size range, so that when mixed with one or more active ingredients and excipients, a flowable mixture is produced. Wilber teaches that the particle size of the granulated polymers is generally falls through 40-45 mesh but retained on 150 or 200 mesh (col. 4, l 44-67). When converted the 40-45 mesh equals 420 microns and 150-200 mesh size equals 75-100 microns. Thus the particle size ranges between 75-420 microns and overlaps with instant 45-425.Wilber also teaches that the over sized particles should be 5% or less and under sized particles should be 25% or less (lines bridging col. 4-5). Wilber teaches that the resulting optimum sized particles obtained are free flowing and are suitable for direct compression. The exemplified compositions of Wilber teach flow rates and compressibility values such as in examples 1-3. Wilber teaches a number of pharmaceutical agents that may be suitable for compressing into tablets including guaifenesin (col. 6, L 54) but does not exemplify guaifenesin.

Troy teaches tablets formed by direct compression from a mixture of an active material such as therapeutic material and as a direct compression vehicle dry, free-flowing, granular sugar and a binder (abstract). Troy teaches free-flowing particles of 12 mesh to 325 mesh (col. 1, L 50-65). Troy states that tablets result in good physical properties and readily dissolve in aqueous media (col. 1 and col. 4, L 1-10). Troy suggests mixing sugar and the binder to effect agglomeration of about 325 mesh (44

microns according to the declaration submitted by applicants on 10-26-07) but not greater than 12 mesh (col. 3, L 7-15 and lines 46-61). Among the active agents, Troy suggests antitussives, but does not explicitly state employing guaifenesin.

It would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made from the teachings of Troy and Wilbur that particle sizes between 12-325 or 20-200 respectively, are important for free flowing and the ability for compression such that the drug is released at a determined rate from the compressed tablet. Troy teaches that sizing of the granules particles is important for free flowing of drug, which in turn imparts improved flow characteristics to the active material and other materials of the blend and also the ease of tabletting. Wilbur suggests particle size ranges between 75-420 microns for free flowability and suitability for direct compression. Troy as well as Dansereau recognizes PVP as a suitable binder for compressible tablets, particularly guaifenesin (Dansereau). Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to employ PVP for the processing and preparation of compressible guaifenesin tablets of Blume because Troy as well as Dansereau recognize PVP as a suitable binder. Further, Dansereau (and Blume) recognizes methylcellulose and PVP as equivalent binders as well as disintegrants in preparing a sustained release compressible tablet preparation comprising guaifenesin.

With respect to the claimed particle sizes, Blume teaches that no more than 30% granulation material passes through 100 mesh (150 microns) and not more than 10% retained on 10-mesh screen (greater than 850 microns). Thus, majority of the particles

of Blume are in the range of 150 microns – 2 mm and a smaller percentage of particles are below 150 microns. A maximum of 30% of the particles that pass through the 100-mesh screen, according to Blume, could be any size below 150 microns (as low as 45 microns claimed in the instant invention). While Blume does not teach the exact percentages of particle sizes claimed in the instant application, there is an overlap in the particle sizes between instant application and that of Blume (150 nm to 425 nm). On the other hand, Wilbur suggests free flowing particles of appropriate size (not too fine a powder or not too oversized) are easy to compress and Troy suggests a particle size of 12 mesh (1.41 mm) to 325 mesh (44 microns) as suitable for free flowing, stable and compressible tablets. Accordingly, a skilled artisan would have readily optimized the particle sizes of the granulated PVP and guaifenesin between 12 mesh and 325 mesh sizes such that the particles have an optimum flow rate, strength and stability and yet do not show capping.

For the claimed additives such as glidants, lubricants, silica, stearic acid etc., Blume and Dansereau teach the conventional excipients including lubricants such as magnesium stearate, calcium stearate etc; binders such as povidone (polyvinylpyrrolidone), gelatin, starch; glidants such as talc or silicon dioxide, stabilizers and other excipients such as lactose, sorbitol etc. Accordingly, in the absence of evidence to the criticality of the specific excipients and their amounts (claims 3-4 & 33-34), it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to the choose the appropriate excipient and optimize the amounts of the same in the composition of Blume with an expectation to obtain tablets

of desired compressibility or hardness and very less friability because the cited prior art desires the same features.

(10) Response to Argument

Appellant argues that Blume teaches a two portion tablet with hydroxypropyl methyl cellulose (not polyvinylpyrrolidone) and that Blume is not concerned with improving the properties of guaifenesin tablets to exhibit low friability, high hardness and resistance to capping. It is argued that the granulation of Blume is quite unlike the instant invention because Blume uses screen sizes rather than particle size distribution, in which 10% have been retained on 10 mesh screen (200 microns) that is substantially larger than the largest particle sizes claimed (0% greater than 425 microns) and more than 60% of Blume's particle sizes lies within the range of 150 -200 nm, which is not equivalent to the ranges claimed in the claim 37. Appellants argue that only the claimed limitations can produce a tablet under relatively low pressure, which exhibits less than 1% friability and hardness in the range of 10.3 to 17.0 kp and is resistant to capping. It is argued that Blume states that the resulting formulation "may further be compressed on a table compressing machine using tooling to form tablets (column 8, lines 36-37)", but does not contain any disclosure of the pressure of the tabletting press, nor of the resulting tablet hardness, capping and friability can be found in Blume.

Appellants argue that examiner's attempt to cobble together the teachings of Dansereau and Troy/Wilbur do not establish prima facie case of obviousness. It is argued that Dansereau, like Blume, contains no disclosure of the tabletting conditions or the particle size distributions, and at best teaches a combination of guaifenesin and

PVP binder. Appellants argue that Wilbur reference does not teach agglomerates of guaifenesin and binder of instant particle size and instead teaches the particle size of the rheology modifying agent. It is argued that the particles of the rheology modifying polymer fall through 40 mesh but retained on 200 mesh. Appellants argue that Wilbur does not disclose the particle size of the resulting polymer and drug blend and hence lacks the claimed agglomerate of active and rheology modified polymer. It is argued that the reference fails to teach particulate guaifenesin and that when the prior art does describe the blending of the guaifenesin and binder, his disclosure is fatally defective as to the particle size of any resulting agglomeration of guaifenesin and binder, is silent as to the parameters upon which the tableting press operates and clearly does not specify the conditions recited in the claims and is similarly silent as to the properties of the resulting tablet. Appellants argue that Troy is only concerned with sugar tablets and not claimed guaifenesin at 85%-97.5%. It is argued that examiner attempted to find bits and pieces of the invention from the collection of art that the examiner searched, which still does not establish the instant limitations. It is argued that Troy teaches 1.68 mm to 44 microns, whereas instant claims require a specific range, particularly for guaifenesin and not sugar (of Troy).

Appellants' arguments are not persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection of record explained the deficiencies of each of the cited references. All of the cited prior

art pertains to the field of tablet making by granulation and compression. The cited references also desire the production of free flowing tablettable powders for preparing compressible tablets of appropriate hardness (Blume). The combination of guaifenesin and polyvinylpyrrolidone is clearly taught by Dansereau et al reference, which also teaches that the two are blended, granulated and passed to a mesh of specific screen size (though not of the same size as claimed in the instant claims). Thus, granulating PVP and guaifenesin together and screening for desired particle sizes is not unknown according to Dansereau et al reference. Blume also teaches blending the claimed drug with a hydrophilic polymer, granulating and screening (col. 4, L 4-15). While the examiner agrees that Wilbur only teaches particle sizes of the rheology modifying polymer and not of the drug, a skilled artisan provided with the disclosure of Blume et al and Dansereau et al would look to other teachings in the prior art for compression of tablets. A skilled artisan would envisage blending of a binder (methocel or PVP of Blume and/or Dansereau respectively) and an active agent (guaifenesin) before the formation of agglomerates and the screening process, with an expectation to achieve good compression and controlled release of the drug and good physical properties without the problems of capping etc., because Wilbur teaches that particulate of suitable sizes flow freely through a die so that they can be directly compressed. Wilbur also teaches that a granular tabletting mixture is formed by blending said polymer and an active agent and compressed to form a tablet. While Wilbur states that the active need not be granulated, when one used granulated slightly crosslinked rheology modifying polymer (col. 8, l 5-10), this does not constitute a teaching away from granulating the

active, particularly in light of the teachings of Dansereau (example 1) and also Blume (fig. 2), both of which teach combining binder and the active agent for granulating to a desired particle size before compression. In this regard, even though Troy does not teach guaifenesin, Troy suggests blending active agents with sugar agglomerates of 20-80 mesh sizes (80 mesh = 180 microns) for free flowing and ease of tabletting (col. 3, L 16-21, l 50-69 and col. 4, l 1-6). Thus, a skilled artisan would have employed the particle sizes taught by Troy and/or Wilbur in preparing the granulated agglomerates of guaifenesin (Blume or Dansereau) and PVP (Dansereau).

Exemplary rationales that may support a conclusion of obviousness include: Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; "Obvious to try " – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art. KSR, 550 U.S. at ___, 82 USPQ2d at 1396. In the instant case, the prior art cited recognizes free flowability as a function of particle size. A skilled artisan would have been motivated to maintain the particle size of not only the binder but also the entire granulated mixture to an optimum size so as to achieve the desirable flow for optimum compression in to tablets. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Appellants' arguments regarding the tabletting press, hardness and capping/friability are not persuasive because the limitation "and is tableted in a tableting press operating at no more than 2.5 tons, to produce tablet exhibiting less than 1% friability, a hardness in the range of 10.3 to 17.0 kp and resistant to capping" constitute process limitations, whereas the claims as such are directed to a product. However, Blume teaches compressing the granulation in to a tablet in a tablet press such that the hardness is 15-30 SCU (1Strong Cobb Unit = 0.71 kilo pound). Appellants have not shown that the tablets resulting from the teachings of Blume, having a particle within the claimed size range based on the teachings of Wilbur and Troy do not posses the claimed hardness, friability and resistance to capping. With respect to the results in tablets 2A-2G, it is observed that while compositions of the instant invention do not exhibit capping at any compression force applied, comparative examples 1 and 3 also do not exhibit capping at the highest compression force. For the friability, comparative examples do provide low friability (<1%) even at highest force applied. Thus, it is not clear if the instant compositions provide any unexpected advantage over the comparative compositions. Therefore, the rejections have been maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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